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REVIEW

Clinical and Imaging Features Associated with an Increased Risk of Early and Late Stroke in Patients with Symptomatic Carotid Disease

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WHAT THIS PAPER ADDS

This is a contemporary review of clinical features, clinical scoring systems, and imaging parameters that have been associated with an increased (or decreased) risk of early/late stroke in patients with symptomatic carotid disease. Most, however, require independent validation before they can be applied to clinical practice.

Objective: The aim of this review was to identify clinical and/or imaging parameters that are associated with an increased (decreased) risk of early/late stroke in patients with symptomatic carotid disease.

In the first 14 days: Natural history studies suggest that 8–15% of patients with 50–99% stenoses will suffer a stroke within 72 hours of their index symptom. Currently, there are insufficient validated data to identify highest-risk patients for emergency carotid endarterectomy (CEA), but an increased risk of stroke appears to be predicted by (i) an $ABCD^2$ score of 4–7; (ii) the presence of acute cerebral injury on CT/MRI; (iii) Gray Scale Median (GSM) <15, (iv) spontaneous embolisation on Transcranial Doppler (TCD); and (v) increased fluorodeoxyglucose (FDG) uptake in the carotid plaque on positron emission tomography (PET). A future goal must be to develop predictive algorithms (based on accessible imaging strategies) for identifying acutely symptomatic patients with highly unstable plaques for emergency CEA.

Medium to long term: In the randomised trials, about 70% of patients with symptomatic 70–99% stenoses were stroke-free on "best medical therapy" at 5 years. Clinical predictors of increased stroke risk include (i) male gender; (ii) age >75; (iii) hemispheric symptoms; and (iv) increasing comorbidity. Imaging features associated with increased stroke risk include (i) irregular stenoses; (ii) contralateral occlusion; (iii) increasing stenosis severity, but not subocclusion; (iv) tandem intracranial disease; (v) a failure to recruit intracranial collaterals; (vi) low GSM; (vii) MR diagnosis of intra-plaque haemorrhage; (vii) spontaneous embolisation on TCD; and (viii) increased FDG uptake in the carotid plaque on PET. Clinical/imaging parameters associated with a lower risk of stroke include (i) female gender, especially those with 50–99% stenoses; (ii) ocular symptoms/lacunar stroke; (iii) smooth stenoses; and (iv) chronic subocclusion.

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INTRODUCTION

In 1991, the European Carotid Surgery Trial (ECST) and the North American Carotid Endarterectomy Trial (NASCET) reported that carotid endarterectomy (CEA) reduced the 5-year risk of stroke (compared with best medical therapy [BMT] alone) in patients with 50–99% stenoses who had suffered carotid territory symptoms within the preceding 6 months.[1,2] Since that time, a large amount of research has been published in a wide range of scientific journals, across a broad spectrum of medical disciplines, making it difficult for surgeons to remain appraised of potentially important developments and innovations.

Two areas of clinical practice are currently of particular interest in recently symptomatic patients. First, the risk of stroke in the early period after onset of symptoms appears

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to be much higher than was previously thought, with contemporary natural history studies suggesting that 8—15% of patients with a 50—99% stenosis may suffer a stroke within 72 hours of their index presenting symptom.[3,4] This type of patient was rarely (if ever) randomised within ECST/NASCET and management strategies need to change to deliver interventions as soon as possible after onset of symptoms, accepting that benefit must always be balanced against the potential for increased procedural risk in some patients. It would clearly be advantageous if it were possible to develop and then validate accessible imaging strategies that were capable of identifying a small proportion of patients who would benefit most from emergency CEA or carotid artery stenting (CAS) within 72 hours of onset of symptoms, as opposed to those with a lower immediate stroke risk who could then undergo a delayed intervention.

Second, despite showing significant benefit favouring CEA, pooled data from ECST and NASCET[5] (Table 1) reveal that only 78 strokes would be prevented at 5 years per 1000 CEAs in patients with 50—69% stenoses (i.e. 922 [92%] were ultimately unnecessary), compared with 156 strokes prevented at 5 years in patients with 70—99% stenoses (i.e. 844 [84%] were ultimately unnecessary). Even if the procedural risk could be reduced to zero, the number of strokes prevented at 5 years per 1000 CEAs in patients with 50—69% stenoses would only increase to 162 (i.e. 838 [84%] were still ultimately unnecessary), while only 218 strokes would be prevented at 5 years in patients with 70—99% stenoses if they underwent CEA with a 0% risk (i.e. 782 [78%]) ultimately unnecessary). In short, although any strategy that reduces the procedural risk is to be welcomed, this will have relatively little impact on increasing the overall effectiveness of CEA in terms of late stroke prevention. It would clearly optimise decision-making and minimise exposure to avoidable risk, if clinical and/or imaging algorithms could identify a "high-risk for stroke" cohort in whom to target CEA/CAS. This is particularly important, as the concept of BMT has changed considerably since the 1990s. It is worth remembering that BMT (at the time of ECST/NASCET) was (at best) aspirin and smoking cessation advice. High-dose statins were not available and treatment goals for diabetes and hypertension were very much different to what is considered normal practice today.

The aim of this topical review is to deliver an overview of published data from the randomised trials (RCTs), as well as contemporary, non-randomised studies to inform the reader of clinical features, clinical scoring systems, and imaging strategies that have been shown to predict a greater (or lesser) risk of stroke, both in the hyperacute period after onset of symptoms and in the medium to long term.

THE RANDOMISED TRIALS

Table 1 summarises 5-year stroke rates (including perioperative stroke/death) in a meta-analysis of 6000+ patients randomised to CEA or BMT within ECST, NASCET, and the Veteran's Affairs (VA) Study.[5] While these trials are now somewhat historical and aspects of management have changed considerably (better medical therapy, emergence of carotid artery stenting as an alternative to CEA, declining procedural risks after CEA), there are still important findings from the trials that are worthy of inclusion in this review.

Surgery conferred significant benefit in recently symptomatic patients who had a 50—69% or a 70—99% stenosis, measured using the NASCET method.[5] Surgery conferred no benefit in patients with 0—49% stenoses, or in those with "near-occlusion". Near occlusion was defined as a 90—95% stenosis in the presence of collapse of the distal ICA lumen on angiography.

Patients with 70—99% stenoses gained maximum benefit from CEA, but nearly 70% remained stroke-free on BMT at 5 years. Because >6000 patients were randomised within ECST, NASCET, and the VA trials, it was possible to undertake meaningful subgroup analyses.[5—13] Although these subgroup analyses are historical (i.e. the actual benefits accrued using modern BMT may have lessened the 5-year stroke risks or benefits from CEA), it is likely that the messages (relating to age, gender, plaque irregularity, rapid treatment, etc.) remain relevant in the current era.

Predictive clinical parameters from the RCTs

Table 2 details clinical/imaging parameters that were associated with a significant increase in late stroke in the randomised trials. Surgery conferred incremental benefit with increasing age.[5—7] The highest absolute risk reduction (ARR) was observed in patients aged >75 years (Table 2). The benefit conferred by CEA in patients aged <65 years with 50—99% stenoses was relatively modest (ARR 5.6% at 5 years), compared with 8.6% for patients aged 65—74 years and 19.2% in patients aged >75 years. There was a similar relationship between age and more severe carotid disease. Carotid endarterectomy prevented 74 strokes at 5 years per 1000 CEAs in recently symptomatic patients aged <65 years who had 70—99% stenoses, increasing to 173

Table 1. Pooled individual patient meta-analysis of outcomes from the European Carotid Surgery Trial, the North American Symptomatic Carotid Endarterectomy Trial, and the Veteran's Affairs Study (data derived from Rothwell et al.[5]).

Stenosis severity	5-year stroke risk (%)		ARR in stroke (%)	Stroke prevented per 1000 CEAs
	CEA	BMT		
<30%	18.36	15.71	−2.6	0 @ 5 years
30—49%	22.80	25.45	+2.6	26 @ 5 years
50—69%	20.00	27.77	+7.8	78 @ 5 years
70—99%	17.13	32.71	+15.6	156 @ 5 years
Near-occlusion	22.40	22.30	−0.1	0 @ 5 years

Table 2. Clinical and imaging features that were predictive of a significant increase in late stroke in patients with 50–99% stenoses randomised within ECST and NASCET.

Clinical features	Imaging features
Increasing age[5–7]	Irregular versus smooth plaques[5]
5-year ARR in ipsilateral stroke conferred by CEA versus BMT	5-year ARR in ipsilateral stroke conferred by CEA versus BMT[a]
<65 years = 5.6%; 65–74 years = 8.6%; >75 years = 19.2%	smooth = 8%; irregular = 17%
Recent symptoms[6]	Increasing stenosis severity[5]
5-year ARR in ipsilateral stroke conferred by CEA versus BMT	5-year ARR in ipsilateral stroke conferred by CEA versus BMT
<2 w = 18.5%; 2–4 w = 9.8%; 4–12 w = 5.5%; >12 w = 0.8%	50–69% = 4%; 60–69% = 5.9%; 70–79% = 15.8%; 80–99% = 17.7%; 90–99% = 32.4%; near occlusion = −0.1%
Male versus females[6]	Contralateral occlusion[5]
5-year ARR in ipsilateral stroke conferred by CEA versus BMT	5-year ARR in ipsilateral stroke conferred by CEA versus BMT
males = 11.0%; females = 2.8%	contralateral occlusion = 24%; no occlusion = 13%
Hemispheric versus ocular symptoms[6]	Tandem intracranial disease[9]
5-year ARR in ipsilateral stroke conferred by CEA versus BMT[a]	3-year risk of ipsilateral stroke in medically treated patients with IAD increased with ICA stenosis severity
ocular = 5%; TIA = 15%; stroke = 18%	50–69% = 19%; 70–84% = 29%; 85–99% = 45%
Cortical versus lacunar stroke[11]	No recruitment of collaterals[10]
3-year ARR in ipsilateral stroke conferred by CEA versus BMT	2-year ARR in ipsilateral stroke conferred by CEA versus BMT
non-lacunar stroke = 15%; lacunar stroke = 9%	collaterals recruited = 5%, no recruitment = 19%
Increasing medical comorbidity[2]	
2-year risk of ipsilateral stroke in medically treated patients	
0–5 comorbidities = 17%; 6 = 23%; 7+ = 39%	

ARR = absolute risk reduction; BMT = best medical therapy; CEA = carotid endarterectomy; IAD = intracranial disease; ICA = internal carotid artery.
[a] 70–99% ICA stenoses.

strokes prevented in patients aged 65–74 years, while surgery prevented 289 strokes per 1000 CEAs in patients aged >75 years.[13] This particular subgroup analysis remains relevant in the modern era, if only to remind surgeons (and stroke physicians) that age (alone) should never be used as a reason to withhold CEA.

Males with 50–99% stenoses gained significantly greater benefit from CEA than females[5] (ARR in stroke at 5 years conferred by CEA over BMT was 11% versus 2.8%, respectively). Surgery also conferred a lower overall benefit in patients presenting with ocular symptoms (5-year ARR in stroke conferred by CEA = 5%), compared with TIA (ARR conferred by CEA = 15%) or stroke patients (ARR conferred by CEA = 18%).[5] Patients presenting with cortical stroke gained greater benefit from CEA, compared with those with lacunar stroke (ARR conferred by CEA at 3 years 15% versus 9%, respectively). However, the benefit conferred by CEA in lacunar stroke patients remained statistically significant,[5,11] Interestingly, NASCET also observed that increasing medical-comorbidity (at baseline) was associated with an *increased* risk of late stroke in medically treated patients, which was not observed in patients with a similar number of comorbidities who were randomised to CEA.[2] In their original report, NASCET analysed 2-year rates of ipsilateral stroke, relative to the presence/absence of certain baseline comorbid features including age >70, male gender, systolic BP >160 mmHg, diastolic BP >90 mmHg, neurological event <30 days, stroke at presentation, stenosis >70%, irregular stenoses and whether there was a past history of cardiac failure, myocardial infarction, hypertension, hyperlipidaemia, diabetes, claudication, and smoking. Surgically treated patients with 0–5 comorbid features had a 2-year risk of ipsilateral stroke of 11%, declining to 8% in those with 7+ comorbidities. By contrast, medically treated patients with 0–5 baseline comorbid features had a 17% risk of ipsilateral stroke at 2 years, increasing to 39% in those with 7+ comorbidities.[2]

One of the most important findings, however, from the combined ECST, NASCET, and VA data was that CEA conferred maximum benefit if performed sooner (rather than later) after onset of symptoms[5,6,13,14] (Table 3). Patients (male and female) with a recently symptomatic 50–

Table 3. Ipsilateral carotid territory ischaemic strokes prevented per 1000 CEAs at 5 years stratified for gender, stenosis severity, and delay from randomisation to surgery (derived from a reanalysis of data from Rothwell et al.[6,14]).

Time from randomisation	50–69% stenosis			70–99% stenosis		
	All	Males	Females	All	Males	Females
<2 weeks	148	152	138	230	235	417
2–4 weeks	33	68	−57	159	238	66
4–12 weeks	4	50	22	79	183	−22
>12 weeks	−2.9	63	−120	74	204	−24

99% stenosis undergoing CEA <2 weeks of randomisation had 148 strokes prevented/1000 CEAs at 5 years (ARR 14.8% at 5 years). Randomisation usually occurred within 1 week of symptom onset (Peter Rothwell, personal communication). However; if surgery was delayed beyond 12 weeks, there was little evidence that any female patient with a moderate stenosis benefitted from surgery. Patients with 70—99% stenoses who underwent CEA <2 weeks of randomisation had 230 strokes prevented/1000 CEAs at 5 years (ARR 23%), compared with only 74 if surgery was delayed >12 weeks (ARR 7.4%). In addition, there was clear evidence of a difference in benefit according to gender. Males continued to gain benefit from CEA, even if their operation was delayed out to 12 weeks (Table 3). By contrast, the benefit conferred by CEA in females was almost exclusively limited to those undergoing rapid surgery, with no apparent evidence of benefit after 4 weeks had elapsed.[6,13,14]

An increasing number of modern practice guidelines now use a 14-day threshold for delivering CEA,[15,16] while some have advocated a 48-hour threshold for treatment.[17] Those who still believe that delivering CEA within a 6-month threshold remains acceptable may wish to reflect on an alternative analysis of "delay data" from the ECST. Centres who performed CEA in patients with 70—99% stenoses within 50 days of onset of symptoms conferred an ARR in stroke (compared with BMT) of 23.6% (95% CI 13.7—33.5). This compares with an ARR of only 6.2% (95%CI −4.3—16.6) in those centres where interventions were delivered after more than 50 days had elapsed.[18] It is a salutary fact, therefore, that had 'slower' centres dominated the randomised trials, CEA would probably not have shown significant benefit.

Predictive imaging parameters from the RCTs

A number of imaging features were associated with an increased risk of late stroke in the RCTs[5,8—10,13] (Table 2). Plaque irregularity was associated with significantly higher rates of ipsilateral stroke in patients randomised to BMT, compared with smooth stenoses. Surgery prevented about 100 strokes/1000 CEAs at 5 years in patients with smooth stenoses, irrespective of whether the underlying stenosis was 75%, 85%, or 95% (10% ARR). By contrast, surgery prevented about 200 strokes/1000 CEAs at 5 years in patients with an irregular 75% stenosis (20% ARR), increasing to 325 strokes prevented in patients with 85% irregular stenoses (ARR 32.5%) and 541 strokes prevented/1000 CEAs at 5 years in patients with an irregular 95% stenosis.[5,8,13] When the RCTs recruited their patients, stenosis measurement was based on intra-arterial angiography. This imaging modality is now never used in routine clinical practice and it remains to be seen whether an ultrasound or MR/CTA diagnosis of plaque irregularity is capable of providing similar prognostic information.

Late stroke increased with stenosis severity, but not near-occlusion.[5] This was an important finding, as "near-occlusion" was previously thought to be a high-risk feature for stroke. The ARR in ipsilateral stroke at 5 years conferred by CEA was 4% for patients with 50—59% stenoses, 6.0% for patients with 60—69% stenoses, 15.5% for patients with 70—89% stenoses, and 32% for patients with 90—99% stenoses. Patients with chronic, near-occlusion gained no benefit from CEA. The reader should, however, exercise caution before excluding all patients with suspected "near-occlusion" from intervention. Most patients randomised within ECST/NASCET had a considerable time delay between symptom and surgery. In the modern era of intervening in the hyperacute period after onset of symptoms (see later), it is not uncommon to find that Duplex ultrasound may give misleading findings when performed very soon after the index event.[19] Despite the presence of high peak systolic velocities across the stenosis, the sonographer may not be able to easily visualise a lumen above the lesion (usually a warning sign that there may be a near-occlusion). Corroborative imaging (CTA/MRA) will nearly always show that the ICA above the plaque is widely patent and amenable to reconstruction.[19] The key clue is the presence of high velocities across the stenosis, as opposed to the high-resistance low systolic velocities (and absent end-diastolic flow) usually seen in patients with a "conventional" near occlusion.[19]

The presence of contralateral occlusion is associated with a significant increase in the risk of late stroke *ipsilateral* to the treated ICA stenosis in medically treated patients.[12,13] Surgery prevented 179 strokes at 2 years per 1000 operations in patients with 70—99% stenoses in the presence of a <70% contralateral stenosis, increasing to 200 in patients with a contralateral 70—99% stenosis. CEA conferred maximum stroke prevention in patients with contralateral occlusion (476 strokes prevented per 1000 operations).

Finally, tandem intracranial disease and a failure to recruit intracranial collateral pathways were associated with a significant increase in late stroke in patients randomised to medical therapy (Table 2). Interestingly, neither intracranial disease, nor a failure to recruit collaterals was associated with an increase in late stroke in patients randomised to CEA.[9,10]

ECST-2

Rothwell developed an algorithm, based on regression analysis from the ECST/NASCET subgroup analyses, for predicting the 5-year risk of stroke in medically treated symptomatic patients with 50—99% stenoses, based on (i) stenosis severity; (ii) plaque irregularity; (iii) clinical presentation; (iv) age; and (v) delay from most recent symptom.[20] The predicted 5-year rates of stroke for medically treated patients ranged from <10% to >50% (Fig. 1). The effectiveness of this algorithm in identifying a low to medium risk cohort of symptomatic patients with 50—99% stenoses (i.e. who might be treated medically in the future) is currently being evaluated in the ECST-2 randomised trial (www.ecst-2.com). Altaf et al. have recently reported that this algorithm was not able to predict patients at higher risk of suffering recurrent neurological events within a median

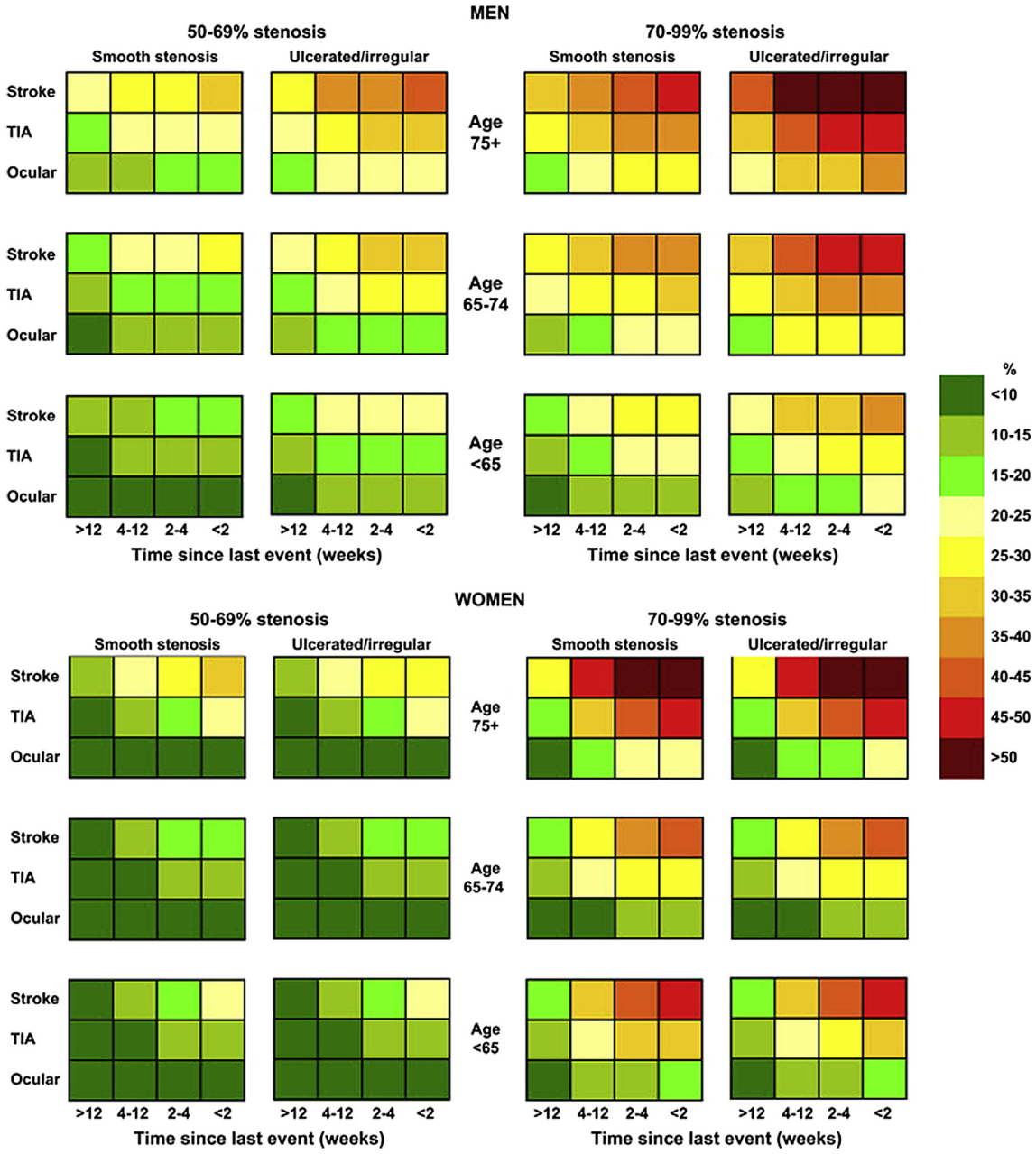

Figure 1. Predicted 5-year absolute risk of ipsilateral ischaemic stroke on medical treatment in ECST patients with recently symptomatic carotid stenosis derived from a Cox model based on six clinically important patient characteristics. Reproduced with permission from Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. From subgroups to individuals: General principles and the example of carotid endarterectomy. Lancet 2005;365:256—265.

of 30 days after onset of symptoms,[21] although (to be fair) the algorithm was never actually designed to identify high- or low-risk patients within the first few weeks.

PREDICTING EARLY/LATE STROKE RISKS

The next sections provide an over-view of clinical features, clinical scoring systems and imaging parameters from non-randomised studies that have been associated with an increased (or decreased) risk of stroke in the (i) hyperacute period after onset of symptoms; (ii) in the first 90 days; and (iii) long term. Most (with the exception of the ABCD^2 score) have not been subjected to independent validation.

Predicting stroke in the first 14 days after onset of symptoms

CEA confers maximum benefit if performed sooner, rather than later (Table 3), and there is also compelling evidence that the early "natural history" risk of stroke after suffering a TIA is higher than previously thought. Pooled data from the ECST/NASCET/VA studies reported a 21% 5-year risk of stroke in patients with 50—99% stenoses who were randomised to BMT[5] (Table 4). However, this 21% risk of stroke at 5 years is at complete variance with the findings of seven contemporary, natural history studies in TIA patients with 50—99% stenoses, where the risks of recurrent stroke were

Table 4. Risk of stroke in the hyperacute period after the index TIA in patients with 50—99% carotid stenoses compared with pooled data from the randomised trials.

	48 hours	72 hours	7 days	14 days	5 years
ESCT + NASCET + VA[5] medical therapy					21%
Fairhead 2005[22]				20%	
Purroy 2007[23]			10%		
Ois 2009[4]		17%	22%	25%	
Bonifati 2011[24]	8%				
Johansson 2013[25]	5%		8%	11%	
Merwick 2013[26]			8%		
Marnane 2014[3]	5%[a]	9%[a]	9%[a]	16%[a]	

[a] Additional data provided by authors (personal communication).

Table 5. The ABCD2 scoring system (derived from Johnstone et al.[30]).

	Parameter	Score
Age	>60 years	1
	<60 years	0
Blood pressure	BP >140/90 mmHg	1
	BP <140/90 mmHg	0
Clinical presentation	Unilateral leg weakness	2
	Speech impairment	1
	Retinal	0
Duration of symptoms	≥60 minutes	2
	10—59 minutes	1
	<10 minutes	0
Diabetes mellitus	Yes	1
	No	0

prospectively documented immediately after onset of symptoms.[3,4,22—26] These more recent studies observed that the risk of stroke in the hyperacute period was 5—8% at 48 hours,[3,24,25] 17% at 72 hours,[3,4] 8—22% at 7 days,[3,4,24—26] and 11—25% at 14 days[3,22,24,25] (Table 4). Additional support for the plaque being acutely unstable in the early period after onset of symptoms comes from two recent audits where (despite the early introduction of BMT), 11—13% of CEA patients suffered recurrent symptoms prior to expedited CEA; a clear reflection of the unstable nature of the underlying plaques.[27,28]

The most obvious explanation for the discrepancy between the 21% 5-year stroke risk on medical therapy in the RCTs and the 20—25% stroke risk at 14 days in the natural history studies is that the randomised trials recruited most of their patients some time *after* the highest risk period for stroke had elapsed, that is the randomised trials recruited a completely different cohort to those now being reported in contemporary, natural history studies.

Accordingly, there is an important cohort of extremely "high risk for stroke" patients who previously missed out on interventions (because they suffered their stroke before having a chance to be treated) who now require emergency/expedited interventions. It is, therefore, imperative that practices should change in order that aggressive BMT and urgent/emergency CEA can be delivered to the highest risk patients in the first few days after onset of symptoms. This is quite a logistical undertaking and it would clearly be beneficial if there were validated algorithms for triaging the highest risk patients for emergency CEA, as opposed to deferred CEA. Interestingly, a parallel change in practice has already occurred in patients with acute ST-segment elevation myocardial infarction, with a drive towards undertaking primary coronary angioplasty/stenting as soon as possible after onset of symptoms.[29]

Clinical scoring systems for predicting early recurrent stroke.

ABCD² score and its modifications

The ABCD² score[30] is a simple bedside scoring system that was developed for TIA patients seen in primary care (Table 5), based on age, blood pressure, clinical presentation, duration of symptoms, and presence/absence of diabetes. The score ranges from 0 to 7.

An ABCD² score of 0—3 is associated with a 1% risk of stroke at both 48 hours and 7 days. Patients with an ABCD² score of 4—5 had a 4% risk of stroke at 48 hours, increasing to 6% at 7 days, while an ABCD² score of 6—7 was associated with a 48-hour stroke risk of 8%, increasing to 12% at 7 days.[30] It is not logistically possible to see every suspected TIA patient within 24 hours of onset of symptoms and, accordingly, most rapid-access TIA clinics triage their patients using the ABCD² score. Patients with an ABCD² score of 0—3 are seen within 7 days, with protocols advising that all patients be started on aspirin and a statin before being seen in the clinic. Higher-risk patients (ABCD² score 4—7) are started on antiplatelet and statin therapy and are then triaged to be seen within 24 hours. One might have expected that a high ABCD² score would also be associated with a higher prevalence of significant carotid disease on Duplex ultrasound. However, that has not been found to be the case.[31]

In the first modification to the ABCD² score, it was hypothesized that the inclusion of acute cerebral infarction on CT/MRI might identify a subgroup of higher-risk patients. This became known as the ABCD²-I score[32] (I denoting imaging; Table 6). Note that patients with any ABCD²-I score in the absence of CT/MRI infarction faced a low risk of recurrent stroke at 48 hours and 7 days. By contrast, the 7-day risk of stroke increased to 9—15% in patients with an ABCD²-I score of 4—7 in the presence of acute infarction.

Further revisions to the ABCD² and ABCD²-I scoring systems were prompted by awareness that early stroke was increased in patients presenting with (i) a dual TIA (defined as a TIA preceded by another TIA within the preceding 7 days); and (ii) a 50—99% stenosis of the ipsilateral internal carotid artery. The revised ABCD³ scoring system allocated 2 points for dual TIA (maximum ABCD³ score = 9), while the ABCD³-I score added 2 points for acute infarction on CT/MRI and 2 points for a >50% carotid stenosis (maximum ABCD³-I score = 13).[33] Table 6 indicates how these modifications influenced 7-day stroke rates. In essence, the higher the score, the greater the 7-day risk of stroke. However, at first sight, there does not seem to be much advantage in knowing whether there was a significant carotid stenosis in addition

Table 6. The ABCD^2, ABCD^2-I, ABCD^3 and ABCD^3-I scoring systems for predicting early stroke after a TIA.

Scoring system	Stroke risk after TIA	
	48 hours	7 days
ABCD^2 0–3[31]	1.0%	1.2%
ABCD^2 4–5[31]	4.1%	5.9%
ABCD^2 6–7[31]	8.1%	11.7%
ABCD^2-I 0–3 no infarction[33]		0.2%
ABCD^2-I 4–5 no infarction[33]		1.4%
ABCD^2-I 6–7 no infarction[33]		3.3%
ABCD^2-I 0–3 acute infarction[33]		2.3%
ABCD^2-I 4–5 acute infarction[33]		8.9%
ABCD^2-I 6–7 acute infarction[33]		15.0%
ABCD^3 0–3[34]		1.0%
ABCD^3 4–5[34]		2.5%
ABCD^3 6–9[34]		11%
ABCD^3 I 0–3[34]		1.0%
ABCD^3-I 4–7[34]		4.0%
ABCD^3-I 8–13[34]		10%

to the presence of acute cerebral infarction. The most likely reason for this discrepancy is because of a paucity of carotid stenosis data. Most TIA patients underwent MRI/CT within 48 hours of symptom onset, but relatively few underwent a carotid scan during this very early time period (i.e. absence of evidence is not evidence of absence).

Imaging and the prediction of early recurrent stroke. Numerous studies have correlated imaging-based features with the presence/absence of a "vulnerable" carotid plaque, but very few have demonstrated whether these plaque features were then associated with an increased risk of stroke during early or late follow-up.

Marnane reported that 27% of first-ever TIA patients with 50–99% stenoses suffered a recurrent stroke within 28 days of symptom onset and correlated patterns of plaque histology with those who did (and did not) suffer an early recurrent stroke.[3] One-fifth of recurrent strokes occurred within 48 hours of the index event, 33% happened within 7 days, while two-thirds occurred within 14 days. Marnane observed that the plaques of patients with early recurrent stroke had histological features consistent with marked plaque instability, including extensive macrophage and lymphocyte infiltration, low fibrous content, extensive fibrous cap disruption, and neovascularisation. After multivariate analysis; the only independent predictor for early recurrent stroke was heavy macrophage inflammation.[3] Interestingly, more traditional "plaque instability" features such as a lipid rich core, luminal thrombus, and intraplaque haemorrhage (IPH), were not associated with an increased risk of recurrent stroke.[3]

The key issue, therefore, will be whether it is possible to develop validated (but above all) accessible imaging strategies for identifying "high-risk for stroke" patients with acutely unstable plaques shortly after admission. To date, very few studies have specifically looked at this role.

Computerised carotid plaque ultrasound

Salem reported that the presence of a large lipid core and a GSM <25 were predictive of a significantly increased risk of recurrent neurological events in the 48–72 hour period prior to expedited CEA, where patients underwent surgery within a median of 8 days of the index symptom.[27] In a subsequent study involving blinded computerised ultrasound plaque analysis and blinded histological assessment of 126 CEA specimens, Salem observed (following logistic regression) that two computerised plaque features were associated with a high probability of there being a histologically unstable carotid plaque: (i) plaque area >95 mm^2; and (ii) a juxta-luminal black area (JBA) >6 mm^2. When these plaque features were present together, there was a 90% probability of an unstable plaque on blinded histology.[34] To date, this algorithm has not been tested in an independent cohort. Russell et al. showed that plaque echolucency is lowest when measured <30 days of the index symptom (mean GSM 13), increasing to 22 at 31–90 days and 33 by 91–180 days,[35] suggesting progressive plaque remodelling and stabilisation Interestingly, this group also observed that the GSM was significantly lower (GSM $= 15$) in patients with histologically unstable plaques, compared with histologically stable plaques (GSM $= 32$, $p = .01$).

MRI

A number of studies have reported on the ability of MR to predict patients at higher (or lower) risk of suffering a stroke in the medium term (30–90 days) or in the long term. Unfortunately, no-one has reported MRI-derived plaque features that can identify patients at highest risk of suffering a recurrent stroke in the first few days after onset of symptoms. An MRI diagnosis of IPH is, however, predictive of increased spontaneous embolisation during the dissection phase of CEA,[36] which does reflect plaque instability.

In a group of patients undergoing MRI within 48 hours of their index cerebral event, Lindsay observed that MR features associated with a Type VI American Heart Association (AHA) unstable plaque (intra-plaque haemorrhage [IPH], fibrous cap rupture, or mural thrombus) were present in 54% of patients, compared with 20% of asymptomatic subjects.[37] While there was no mention of any correlation between Type VI plaques and recurrent stroke, 78% of patients in the acutely symptomatic group had an average of seven ischaemic lesions on diffusion weighted imaging (DWI). There was no association between AHA plaque type and the prevalence of acute DWI lesions, but an MRI diagnosis of fibrous cap rupture was associated with a higher burden of DWI lesions.[37] This is clearly an area where carefully designed MRI studies could inform the literature.

Transcranial Doppler ultrasound (TCD) diagnosed embolisation

In a series of 123 recently symptomatic patients undergoing expedited CEA, Salem observed that 43% of patients who

underwent CEA within 7 days of the index event had spontaneous, preoperative embolisation on TCD, compared with 22% who underwent CEA between days 8 and 14 and 16% in whom surgery was performed >14 days after the index event.[38] Almost a quarter (23%) of patients with spontaneous embolisation suffered a recurrent neurological event in the 48–72-hour period prior to expedited CEA, compared with 11% of patients with no embolisation. The key question remains as to what is the optimal duration of TCD monitoring. In Salem's study, patients were monitored for only 30 minutes, which is probably too short for TCD diagnosed embolisation to be validated as being a method for identifying high risk for stroke patients in the first few days after onset of symptoms.

Positron emission tomography (PET)

Positron emission tomography (PET) tracers accumulate within metabolically active cells. Fluorodeoxyglucose (FDG) is a glucose analogue that actively competes with glucose for uptake in macrophages, which will have increased rates of glycolysis within the core of an unstable plaque. Because FDG is not metabolised, it accumulates within the activated macrophages. Marnane performed FDG-PET uptake studies in 60 recently symptomatic patients and showed that patients with the highest tertile mean standardised uptake value (SUV) of FDG in the ipsilateral (symptomatic) internal carotid artery plaque had higher rates of early recurrent stroke.[39] Graebe et al. showed an inverse relationship between plaque GSM and FDG uptake. Echogenic plaques had lower FDG uptake (suggesting less inflammation and greater plaque stability). Interestingly, there was much more variability in the relationship between FDG uptake and the GSM, that is low GSM (echolucent) plaques displayed a range of inflammatory activity.[40]

However, one of the key problems with PET is its limited accessibility and high costs. It is unlikely, therefore, that PET will ever assume a role in routine clinical practice, but it could prove very useful in validating/evaluating other more accessible imaging modalities (e.g. MRI, computerised ultrasound plaque analysis) in identifying features associated with a high risk of early stroke.

Predicting stroke in the first 90 days after onset of symptoms

Spontaneous embolisation on TCD

In a pooled analysis of two prospective databases (123 recently symptomatic patients) with a median 36-day follow-up after onset of symptoms, the presence of spontaneous embolisation was associated with a threefold excess risk of recurrent TIA/stroke (adjusted HR 3.35, 95% CI 1.69–6.67).[22]

MRI

There is stronger evidence correlating MR-derived plaque features with recurrent stroke/TIA in the first 30–90 days after onset of symptoms. Altaf showed that an MRI diagnosis of IPH detected within a median of 19 days after the index event was associated with a significantly increased prevalence of acute and subacute DWI lesions (OR 5.8, 95% CI 1.0–32.8), as well as a significantly higher prevalence of TCD diagnosed spontaneous embolisation.[41] Interestingly (and perhaps counterintuitively), there was no association between spontaneous embolisation and acute DWI lesions.

The same group has also reported that an MRI diagnosis of IPH in recently symptomatic patients with 70–99% carotid stenoses (MR performed within a median of 40 days of the index event) was associated with a significant increase in the prevalence of recurrent neurological events over the next 30 days of follow-up. Cumulative freedom from recurrent events was approximately 85% in patients with no evidence of IPH, compared with 50% in patients with an MRI diagnosis of IPH.[42] In their latest analysis, Altaf et al. reported that patients with a combination of MRI diagnosed IPH and spontaneous embolisation on TCD had the highest rates of recurrent events during follow-up, although absolute risks were not quoted in the paper, possibly because they involved very small numbers.[22]

Positron emission tomography

Marnane performed FDG-PET uptake studies in 60 recently symptomatic patients. The mean standardized uptake value (SUV) of FDG in the ipsilateral (symptomatic) internal carotid artery plaque was significantly higher in patients suffering a recurrent stroke within 90 days of the index event. The authors observed that a mean SUV of 2.14 had 98% specificity and 31% sensitivity for predicting recurrent stroke, with 83% of patients with recurrent strokes being above this SUV threshold.[39]

Predicting late stroke in symptomatic patients

MRI

Teng performed high-resolution MR within 72 hours of the index event in 42 patients with 30–69% carotid stenoses. Twenty-one had an MR diagnosis of juxtaluminal haemorrhage or thrombus (JLH/T), while 21 did not. During 2 years of follow-up, 11/21 patients with JLH/T at baseline (52%) suffered recurrent neurological events, compared with 0/21 (0%) with no evidence of JLH/T.[43]

Hosseini combined data from three prospective databases involving 179 patients with a symptomatic 50–99% carotid stenosis (symptoms <6 months) who underwent high-resolution MR imaging within 6 weeks of the index event.[44] One-hundred and fourteen (64%) had MR evidence of IPH. During a follow-up ranging from 1 day to 9 years, 62 patients suffered recurrent neurological events and 57 (92%) had MR evidence of IPH on the baseline study. Twenty-six patients suffered a recurrent stroke during follow-up and 25 (96%) had an MRI diagnosis of IPH. The cumulative 5-year risk of any recurrent neurological event was 85% in patients with a baseline MRI diagnosis of IPH, compared with only 13% in patients without IPH.[44] Unfortunately, there are no studies looking at serial changes in

MRI diagnosed IPH and whether these correlate with plaque stabilisation or symptoms.

CTA

Magge analysed outcomes in 315 patients suffering a recent stroke who had a <70% carotid stenosis at baseline and who then underwent a second CT angiogram (average 440 days later). They observed that age >75 years, the use of antihypertensive agents and a maximum carotid plaque thickness >4 mm identified 10/14 patients who subsequently suffered a recurrent stroke.[45]

Ultrasound

Gronholdt followed 135 recently symptomatic patients (<6 months of the index symptom) who had 50–99% ICA stenoses and observed that patients with a GSM below a mean of 74 had a mean 4-year risk of ipsilateral stroke of 29% versus 12% for patients with an echogenic (plaque GSM >75). This translates into a threefold excess risk of ipsilateral stroke at 4 years for patients with echolucent plaques (OR 3.1, 95% CI 1.3–7.3), compared with patients with echogenic plaques.[46]

Contrast enhanced ultrasound (CEUS) also provides an accessible assessment of plaque neovascularisation and this has been shown to correlate with spontaneous microembolisation on transcranial Doppler ultrasound.[47] It remains to be seen, however, whether increased neovascularity on CEUS ± a TCD diagnosis of spontaneous embolisation can reliably diagnose a high-risk subgroup for late stroke.

Circulating biomarkers

Although a number of potential circulating biomarkers (in relation to the vulnerable plaque) have been evaluated, very few studies have correlated biomarker activity with late stroke risk in symptomatic patients with carotid disease, possibly because most patients undergo CEA. Lipoprotein associated phospholipase A_2 (Lp-PLA_2) is a macrophage-derived enzyme that metabolises low-density lipoprotein into the pro-inflammatory metabolites lysophosphatidylcholine (LPC) and oxidised fatty acids. Increased levels of Lp-PLA_2 have been found in atherosclerotic plaques associated with thinned or ruptured caps, where this is mostly localised to activated macrophages undergoing apoptosis in the lipid rich necrotic core and fibrous cap.[48] The Northern Manhattan Stroke Study reported that (compared with patients with the lowest quartile of Lp-PLA_2 activity), patients with the highest quartile of LpPLA_2 activity were twice as likely to suffer a late recurrent stroke (OR 2.54, 95%CI 1.01–6.39).[49] It remains unclear whether LpPLA2 activity has any additional predictive value in the acute and long term in patients with significant carotid disease.

IN CONCLUSION

Symptomatic: first 14 days

There is currently a paucity of validated data to enable identification of the highest-risk patients for emergency CEA, but an increased risk of stroke in the hyperacute period appears to be predicted by (i) an $ABCD^2$ score of 4–7; (ii) the presence of acute cerebral injury on CT/MRI; (iii) a GSM <15; and (iv) spontaneous embolisation on transcranial Doppler. This is an important area for future research so that accessible and validated imaging strategies can be used to identify which patients would benefit from emergency (as opposed to deferred) CEA or CAS.

Symptomatic: <90 days and long term

Clinical predictors of increased stroke risk in the intermediate to long-term include (i) male gender; (ii) age >75 years; (iii) hemispheric symptoms; and (iv) increasing comorbidity. Imaging parameters associated with an increased risk of intermediate or late stroke include (i) irregular stenoses, especially with increasing stenosis severity; (ii) contralateral occlusion; (iii) increasing stenosis severity; (iv) tandem intracranial disease; (v) a failure to recruit intracranial collaterals; (vi) low GSM; (vii) an MR diagnosis of IPH; and (viii) increased macrophage uptake of FDG. There are currently few published data linking biomarker activity with an increased risk of late stroke in patients with symptomatic carotid disease. Clinical/imaging parameters associated with a lower intermediate/late risk of stroke include (i) females, especially those with 50–99% stenoses and any delay to treatment; (ii) ocular symptoms/lacunar stroke; (iii) smooth stenoses; and (iv) chronic near-occlusion.

At present, all patients with recently symptomatic 50–99% stenoses are being considered for CEA or CAS. Even if the procedural risk could be reduced to zero, the majority will still undergo an (ultimately) unnecessary intervention. It is to be hoped that future studies will lead to the development of image-based algorithms for identifying a cohort of low- to medium-risk (for stroke) patients who can be treated medically, thereby releasing logistical and financial resources to optimise the delivery of emergency/expedited CEA to the highest-risk patients.

CONFLICT OF INTEREST

None.

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REFERENCES

1 European Carotid Surgery Triallists Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or mild (0–29%) carotid stenosis. *Lancet* 1991;**337**:1235–43.
2 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445–53.
3 Marnane M, Prendeville S, McDonnell C, Noone I, Barry M, Crowe M, et al. Plaque inflammation and unstable morphology are associated with early stroke recurrence in symptomatic carotid stenosis. *Stroke* 2014;**45**:801–6.

4 Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke* 2009;**40**:2727—31.

5 Rothwell PM, Eliasziw M, Gutnikov SA. for the Carotid Endarterectomy Trialists Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107—16.

6 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915—24.

7 Alamowitch S, Eliasziw M, Algra A, Meldrum H, Barnett HJM. for the NASCET Group. Risk, causes and prevention of ischaemic stroke in elderly patients with symptomatic internal carotid artery stenosis. *Lancet* 2001;**357**:1154—60.

8 Eliasziw M, Streifler JY, Fox AJ, Hacjinski VC, Ferguson GG, Barnett HJM. for the NASCET Trial. Significance of plaque ulceration in symptomatic patients with high grade stenosis. *Stroke* 1994;**25**:304—30.

9 Kappelle LJ, Eliasziw M, Fox AJ, Sharpe BL, Barnett HJM. for the NASCET Group. Importance of intracranial atherosclerotic disease in patients with symptomatic stenosis of the internal carotid artery. *Stroke* 1999;**30**:282—6.

10 Henderson RD, Eliasziw M, Fox AJ, Rothwell PM, Barnett HJM. for the NASCET Group. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. *Stroke* 2000;**31**:128—32.

11 Inzitari D, Eliasziw, Sharpe BL, Fox AJ, Barnett HJM. for the NASCET Group. Risk factors and outcome of patients with carotid artery stenosis presenting with lacunar stroke. *Neurology* 2000;**54**:660—6.

12 Baker WH, Howard VJ, Howard G, Toole JF. for the ACAS Investigators. Effect of contralateral occlusion on long term efficacy of endarterectomy in the asymptomatic Carotid Atherosclerosis Study. *Stroke* 2000;**31**:2330—4.

13 Naylor AR. An update on the randomised trials of interventions for symptomatic and asymptomatic carotid artery disease. *Ital J Vas Endovasc Surg* 2006;**13**:111—20.

14 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischaemic attack and non-disabling stroke. *Stroke* 2004;**35**:2855—61.

15 *Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)*. http://www.nice.org.uk/nicemedia/pdf/CG68FullGuideline.pdf [accessed 28.07.14].

16 Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. *Eur J Vasc Endovasc Surg* 2009;**37**:S1—19.

17 The National Stroke Strategy. www.dh.gov.uk/stroke [accessed 28.07.14].

18 Rothwell PM. Treating individuals 1: external validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005;**365**:82.

19 Naylor AR. Practical issues arising from acute carotid interventions. In: *Vascular and endovascular challenges update*. BIBA Publishing; 2013. p. 38—46.

20 Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. From subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet* 2005;**365**:256—65.

21 Altaf N, Kandiyil N, Hosseini A, Mehta R, MacSweeney S, Auer D. Risk factors associated with cerebrovascular recurrence in symptomatic carotid disease: a comparative study of carotid plaque morphology, microemboli assessment and the European Carotid Surgery Trial risk model. *J Am Heart Assoc* 2014;**3**: e000173. http://dx.doi.org/10.1161/JAHA.113.000173.

22 Fairhead JF, Mehta Z, Rothwell PM. Population based study of delays in carotid imaging and surgery and the risk of recurrent stroke. *Neurology* 2005;**65**:371—5.

23 Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke* 2007;**38**:3225—9.

24 Bonifati DM, Lorenzi A, Ermani M, Refatti F, Gremes E, Boninsegna C, et al. Carotid stenosis as predictor of stroke after transient ischemic attacks. *J Neurol Sci* 2011;**303**:85—9.

25 Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *Int J Stroke* 2013;**8**:220—7.

26 Merwick A, Albers GW, Arsava EM, Ay H, Calvert D, Coutts SB, et al. Reduction in early stroke risk in carotid stenosis with transient ischaemic attack associated with statin treatment. *Stroke* 2013;**44**:2814—20.

27 Salem MK, Sayers RD, Bown MJ, West K, Moore D, Nicolaides AN, et al. Patients with recurrent ischaemic events from carotid artery disease have a large lipid core and low GSM. *Eur J Vasc Endovasc Surg* 2012;**43**:147—53.

28 Ali MA, Stephenson JA, Naylor AR. Delays prior to expedited carotid endarterectomy: a prospective audit of practice. *Eur J Vasc Endovasc Surg* 2013;**46**:404—10.

29 www.publications.nice.org.uk/myocardial-infarction-with-st-segment-elevation-cg167 [accessed 05.06.14].

30 Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;**369**:283—92.

31 Walker J, Isherwood J, Eveson D, Naylor AR. Triaging TIA/minor stroke patients using the ABCD2 score does not predict those with significant carotid disease. *Eur J Vasc Endovasc Surg* 2012;**43**:495—8.

32 Giles MF, Albers GW, Amarenco P, Arsava EM, Asimos AW, Ay H. Early stroke risk and ABCD2 score performance in tissue- versus time-defined TIA A multicenter study. *Neurology* 2011;**77**:1222—8.

33 Merwick A, Albers GW, Amarenco P, Arsaya EM, Calvet D, Coutts SB, et al. Addition of brain and carotid imaging to the ABCD2 score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol* 2010;**9**:1060—9.

34 Salem M, Bown M, Sayers RD, Nicolaides A, Robinson T, West K, et al. A model for identifying patients with an unstable carotid plaque using computerised plaque analysis. *Eur J Vasc Endovasc Surg* 2014;**48**:118—25.

35 Russell DA, Wijeyaratne SM, Gough MJ. Changes in carotid plaque echomorphology with time since a neurological event. *J Vasc Surg* 2007;**45**:367—72.

36 Altaf N, Beech A, Goode SD, Gladman JR, Moody AR, Auer DP, et al. Carotid intraplaque hemorrhage detected by magnetic resonance imaging predicts embolization during carotid endarterectomy. *J Vasc Surg* 2007;**46**:31—6.

37 Lindsay AC, Biasiolli L, Lee JMS, Kylintireas I, MacIntosh BJ, Watt H, et al. Plaque features associated with increased cerebral infarction after minor stroke and TIA: a prospective,

case-control, 3-T carotid artery MR imaging study. *JACC Cardiovasc Imaging* 2012;**5**:388—96.
38 Salem MK, Sayers RD, Bown MJ, Naylor AR. Spontaneous embolisation in asymptomatic and acutely symptomatic patients with TIA/minor stroke. *Eur J Vasc Endovasc Surg* 2011;**41**:720—5.
39 Marnane M, Merwick A, Sheehan OC, Hannon N, Foran P, Grant T, et al. Carotid plaque inflammation on 18F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence. *Ann Neurol* 2012;**71**:709—18.
40 Graebe M, Pedersen SF, Hojgaard L, Kjaer A, Sillesen H. 18FDG PET and ultrasound echolucency in carotid artery plaques. *JACC Imaging* 2010;**3**:289—95.
41 Altaf N, Goode SD, Beech A, Gladman JR, Morgan PS, MacSweeney ST, et al. Plaque haemorrhage is a marker of thromboembolic activity in patients with symptomatic carotid disease. *Radiology* 2011;**258**:538—45.
42 Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* 2007;**38**:1633—5.
43 Teng Z, Sadat U, Huang Y, Young VE, Graves MJ, Lu J, et al. In vivo MRI-based 3D mechanical stress-strain profiles of carotid plaques with juxtaluminal plaque haemorrhage: an exploratory study for the mechanism of subsequent cerebrovascular events. *Eur J Vasc Endovasc Surg* 2011;**42**:427—33.
44 Hosseini AA, Kandiyil N, MacSweeney ST, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging strongly predicts recurrent ischemia and stroke. *Ann Neurol* 2013;**73**:774—84.
45 Magge R, Lau BC, Soares BP, Fischette S, Arora S, Tong E, et al. Clinical risk factors and CT imaging features of carotid atherosclerotic plaques as predictors of new incident carotid ischemic stroke: a retrospective cohort study. *AJNR* 2013;**34**:402—9.
46 Gronholdt M-L, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* 2001;**104**:68—73.
47 Zhou Y, Xing Y, Li Y, Bai Y, Chen Y, Sun X, et al. An assessment of the vulnerability of carotid plaques: a comparative study between intra-plaque neovascularisation and plaque echogenicity. *BMC Med Imaging* 2013;**13**:13.
48 Kolodgie FD, Burke AP, Skorija KS, Ladich E, Kutys R, Makuria AT, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2006;**26**:2523—9.
49 Elkind MSV, Tai W, Coates K, Paik MC, Sacco R. Lipoprotein-associated phospholipase A2 activity and risk of recurrent stroke. *Cerebrovasc Dis* 2009;**27**:42—50.